CLINICAL PRACTICE

Hereditary Angioedema

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 19-year-old woman presents to the emergency department with light-headedness, severe abdominal pain, and intractable nausea and vomiting that began 12 hours earlier. The patient reports previous episodes of abdominal pain and swelling of her hands and feet that have been attributed possibly to food allergies, which have recently become more frequent. There is no associated urticaria. Her only medication is an oral contraceptive that was started 3 months earlier. She notes a history of similar episodes in her father. She is afebrile, with a blood pressure of 75/40 mm Hg, a pulse of 120 beats per minute, and diffuse abdominal tenderness with guarding and rebound tenderness. How should her case be evaluated and treated?

THE CLINICAL PROBLEM

Hereditary angioedema, initially described by Osler in 1888, is an autosomal dominant disease caused by a deficiency in functional C1 inhibitor.[1] Hereditary angioedema is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema typically involving the arms, legs, hands, feet, bowels, genitalia, trunk, face, tongue, or larynx (Fig. 1). Its prevalence is uncertain but is estimated to be approximately 1 case per 50,000 persons, without known differences among ethnic groups.[2] Symptoms typically begin in childhood (often as early as 2 or 3 years of age), worsen around puberty, and persist throughout life, with unpredictable severity. Untreated patients have attacks every 7 to 14 days on average, with the frequency ranging from virtually never to every 3 days.[3,4] There is considerable variation in the severity of hereditary angioedema, even within a kindred.[5] Results of observational studies suggest that minor trauma and stress are frequent precipitants of episodes of swelling, but many attacks occur without an apparent trigger.[6] Pregnancy has a variable effect on disease severity, but attacks are rare at the time of delivery. Patients with hereditary angioedema have an increased frequency of autoimmune diseases, especially glomerulonephritis.[7]

Attacks of hereditary angioedema usually follow a predictable course. Many attacks are preceded by a prodrome (usually a tingling sensation), and approximately a third are accompanied by erythema marginatum, a nonpruritic, serpiginous rash. The swelling classically worsens slowly but relentlessly over the first 24 hours, then gradually subsides over the subsequent 48 to 72 hours. The arms, legs, hands, feet, and abdomen are the most common sites of swelling.[4] Oropharyngeal swelling is less frequent, but over half of patients have had at least one episode of laryngeal angioedema during their lifetime.[4] Attacks may start in one location and then spread to another before resolving.

Hereditary angioedema affecting the abdomen or oropharynx can be associated with significant risk of illness and death.[2,6] Abdominal attacks can cause severe abdominal pain, nausea, and vomiting. Bowel sounds are often diminished or si-

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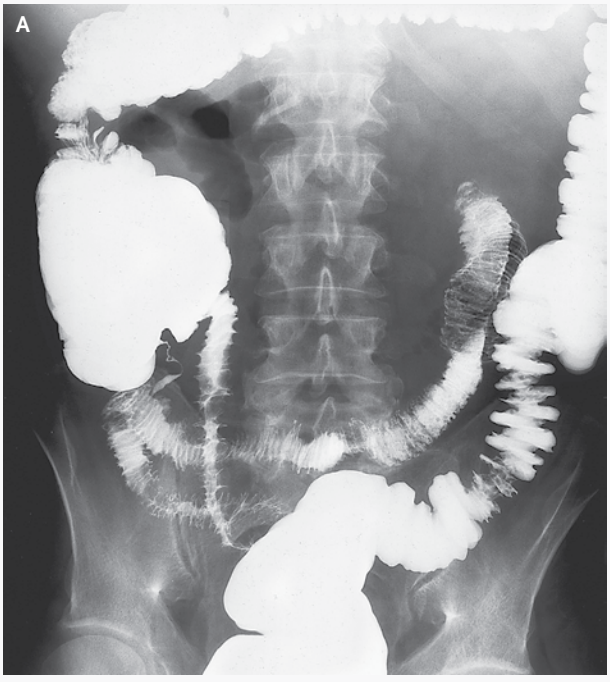

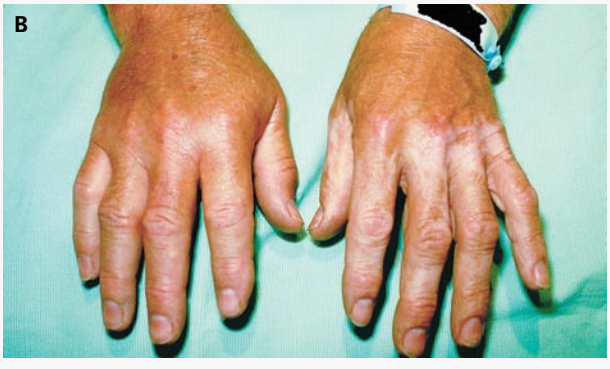

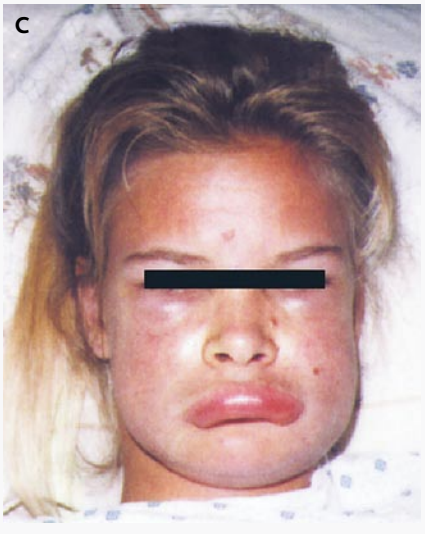

Figure 1. Swelling in Patients with Hereditary Angioedema.

Panel A shows the results of a barium study performed in a patient during an abdominal attack; there is clear evidence of submucosal swelling of the distal wall of the small intestine, with spiculation and thickening of intestinal folds. Panel B shows an example of asymmetric swelling of the hands. Another patient is shown during a facial attack (Panel C).

lent, and guarding and rebound tenderness may be present on physical examination, leading in some cases to unnecessary abdominal surgery. A shift of fluids into the interstitium or peritoneal cavity during abdominal attacks can cause clinically significant hypotension. Laryngeal edema poses the greatest risk for patients with hereditary angioedema; although proper diagnosis and treatment should protect them, historical data have suggested that asphyxiation caused over 30% of deaths among patients with this disease in the past.[6] Even today, patients occasionally die from asphyxiation, particularly in the absence of a proper diagnosis.

Hereditary angioedema results from a mutation in the C1-inhibitor gene.[8] According to the C1-inhibitor gene mutation database (HAEdb, http://hae.enzim.hu), over 150 different mutations have been identified in patients with hereditary angioedema.[9-11] There are two main types of hereditary angioedema: type I (accounting for 85% of cases) and type II (15% of cases). These are indistinguishable in clinical presentation but are caused by different mutations. C1-inhibitor mutations that cause type I hereditary angioedema occur throughout the gene and result in truncated or misfolded proteins that are not efficiently secreted, with decreases in both antigenic and functional levels of C1 inhibitor. Mutations that cause type II hereditary angioedema usually involve exon 8 at or near the active site, resulting in a mutant protein that is secreted but is dysfunctional; antigenic C1-inhibitor levels are normal but functional C1-inhibitor levels are low.

A third type of familial angioedema has also been described,[12,13] in which patients have normal antigenic and functional C1-inhibitor levels. The first description indicated a dependence on increased estrogen levels, with angioedema involving only women, particularly during pregnancy or treatment with exogenous estrogen. Subsequently, kindreds with some affected men have also been described. Clinically, patients with familial angioedema are virtually indistinguishable from those with hereditary angioedema, except that a higher percentage of their attacks are facial.[14] Several but not all kindreds have a gain-of-function mutation in coagulation factor XII that may predict enhanced generation of bradykinin.[15,16]

C1 inhibitor, a member of the serpin family of serine protease inhibitors, is the major inhibitor of several complement proteases (C1r, C1s, and mannose-binding lectin–associated serine protease [MASP] 1 and 2) and contact-system proteases (plasma kallikrein and coagulation factor XIIa) and a relatively minor inhibitor of the fibrinolytic protease plasmin and the coagulation protease factor XIa (Fig. 2).[8] During attacks of hereditary angioedema, these plasma proteolytic cascades are activated, and several vasoactive substances are generated. Studies have shown that bradykinin is the predominant mediator of enhanced vascular permeability in hereditary-angioedema attacks.[17] Bradykinin is a nanopeptide generated by activation of the contact system that can potently increase vascular permeability by binding to its cognate receptor (the bradykinin B2 receptor) on vascular endothelial cells. Consistent with these findings in humans is the demonstration that homozygous C1-inhibitor–knockout mice have a persistent defect in vascular permeability that is dependent on bradykinin.[18]

STRATEGIES AND EVIDENCE

DIAGNOSIS

Delays in diagnosis are common in patients with hereditary angioedema. The average time between the onset of symptoms and the diagnosis was 22 years as of 1977 and was still more than 10 years as of 2005.[6,19] The diagnosis should be suspected in any patient who presents with recurrent angioedema or abdominal pain in the absence of associated urticaria. Although most patients report a family history of angioedema, up to 25% have a de novo C1-inhibitor mutation.[20] The differential diagnosis and major distinguishing features of hereditary angioedema are described in Table 1.

Laboratory testing is needed to confirm or rule out the diagnosis. Virtually all patients with hereditary angioedema have a persistently low antigenic C4 level with normal antigenic C1 and C3 levels.[20,21] Measurement of C4 levels is a cost-effective screening test to rule out hereditary angioedema, although in rare cases, the C4 level is normal between attacks.[21] Subsequent measurement of antigenic and functional C1-inhibitor levels confirms the diagnosis of hereditary angioedema and distinguishes between type I (low antigenic and functional C1-inhibitor levels) and type II (normal antigenic C1-inhibitor level but low functional C1-inhibitor activity).[22,23] In rare cases, patients with inherited angioedema have normal functional C1-inhibitor levels; some but not all of these patients are found to have a factor XII mutation.

MANAGEMENT

Optimal management of hereditary angioedema includes treatment of acute attacks, short-term prophylaxis to prevent an attack, and long-term prophylaxis to minimize the frequency and severity of recurrent attacks.

Short-Term Treatment

Purified C1-inhibitor replacement therapy has been shown to be highly effective and without serious adverse effects in randomized, controlled trials.[24,25] It is the main treatment for acute attacks of hereditary angioedema in many countries.[26-29] Attacks typically begin to resolve within 30 to 60 minutes after intravenous injection of C1 inhibitor (500 to 2000 U).[26-29] However, C1-inhibitor replacement therapy is not currently approved in the United States.

There are no other approved or well-studied treatments for acute attacks of hereditary angioedema, although various interventions have been suggested. Fresh-frozen plasma contains C1 inhibitor, and several uncontrolled studies have reported a benefit of its use in acute attacks of hereditary angioedema.[30] However, such use is controversial because fresh-frozen plasma also contains contact-system proteins that may provide substrate for additional generation of bradykinin, which could exacerbate attacks in some patients. This is a particular concern in patients

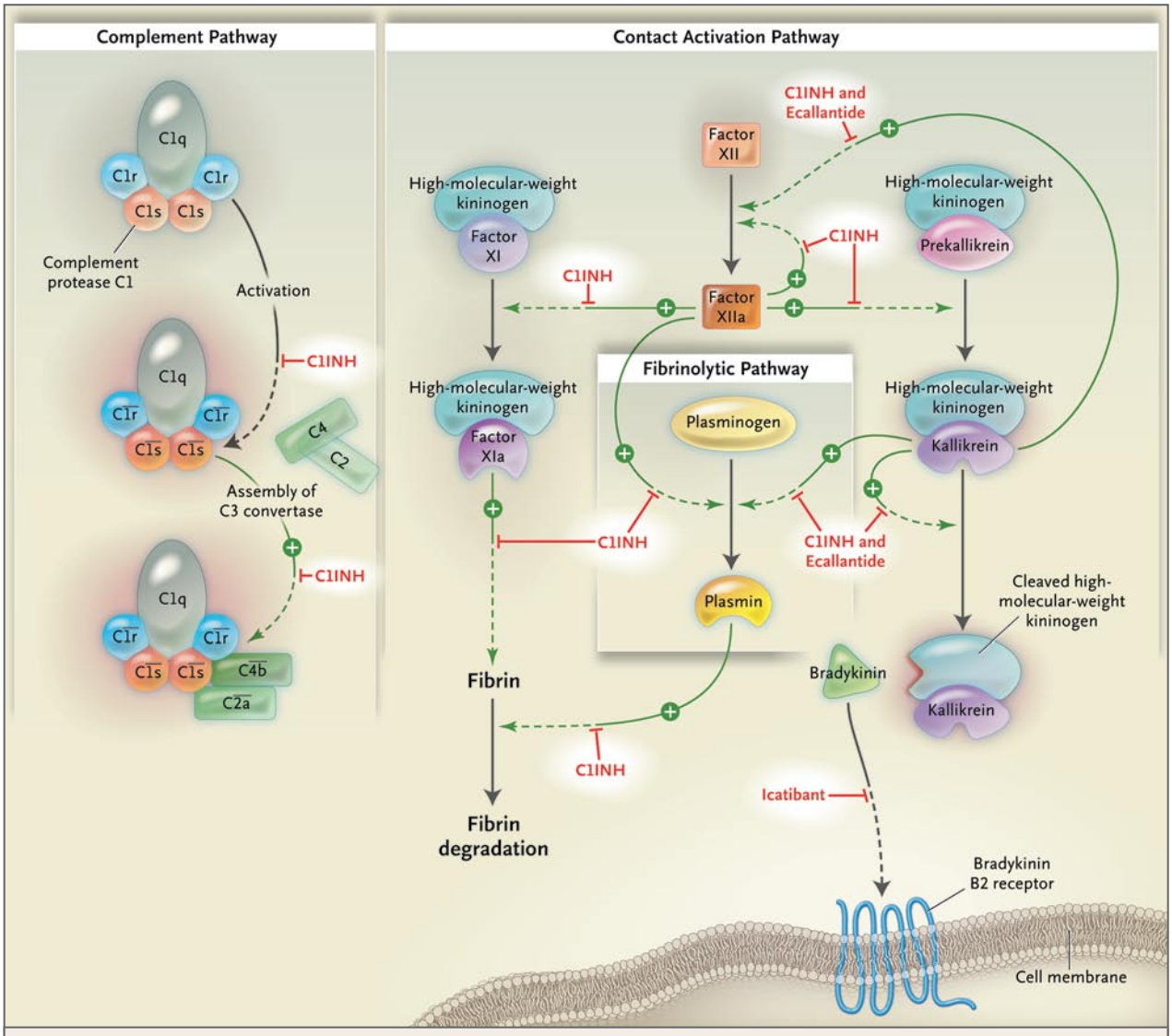

Figure 2. Pathways Inhibited by C1 Inhibitor (C1INH) and New Drugs.

In the classic complement pathway, the complement protease C1 is activated and then assembles the C3 convertase. (Activation is indicated by horizontal bars over the complement names.) In the contact activation pathway, trace amounts of factor XIIa activate additional factor XII, as well as prekallikrein. Activated factor XIIa activates factor XI to factor XIa, leading to enhanced fibrin formation. Activated factor XIIa and kallikrein activate each other, and then plasma kallikrein cleaves high-molecular-weight kininogen to release bradykinin. In the fibrinolytic pathway, plasminogen is activated to plasmin, which cleaves fibrin. Proteolytic activities are indicated with green arrows and point toward the steps they catalyze. Steps inhibited by C1INH, through conventional or new types of therapy, or by two other new drugs being investigated for the treatment of hereditary angioedema are shown with red T bars.

with laryngeal angioedema, who may require emergency intubation if the swelling worsens.

Clinical experience indicates that epinephrine may provide a transient benefit, occasionally (but not predictably) obviating the need for intubation.[31] Neither corticosteroids nor antihistamines have been shown to provide a meaningful benefit during attacks of hereditary angioedema and should not be used for this indication. Although 17α-alkylated androgens and antifibrinolytic drugs are efficacious in preventing attacks of hereditary angioedema, they do not become effective for several days, making them unsuitable for short-term treatment.

Symptomatic control is currently the cornerstone of therapy in the United States. Manage-

Table 1. Clinical and Laboratory Findings Associated with Angioedema of Various Causes.*

Type of Angioedema	Clinical Findings	Laboratory Findings				
		C4 Level	Antigenic C1-Inhibitor Level	Functional C1-Inhibitor Level	C1q Level	C3 Level
Hereditary angioedema	Recurrent angioedema and abdominal attacks without urticaria; attacks are episodic, with intervals between periods of swelling; onset in childhood or young adulthood, with worsening around the time of puberty; prolonged attacks (typically 72–96 hr in duration); family history in 75% of patients; attacks do not respond to antihistamines or corticosteroids	Decreased	Decreased (in type I) or normal (in type II)	Decreased	Normal	Normal
Acquired C1-inhibitor deficiency	Attacks similar to those in hereditary angioedema; onset in middle age or later; absence of family history; attacks do not respond to antihistamines or corticosteroids	Decreased	Decreased or normal	Decreased	Decreased	Normal or decreased
Inherited angioedema with normal C1-inhibitor levels	Family history of angioedema; possible preponderance of women among affected persons; may be estrogen-dependent; typically manifested after childhood; face, tongue, and extremities affected more than abdomen; attacks do not respond to antihistamines or corticosteroids	Normal	Normal	Normal	Normal	Normal
ACE-I–associated angioedema	History of ACE-I use; angioedema tends to affect face and tongue; more common in blacks and smokers than other subgroups; patients can usually tolerate angiotensin-receptor blockers	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Angioedema sometimes accompanied by urticaria; swelling typically lasts up to 48 hr; attacks may occur daily; attacks relieved with antihistamines or corticosteroids	Normal	Normal	Normal	Normal	Normal
Allergic angioedema	Angioedema usually accompanied by urticaria and sometimes anaphylaxis; may be pruritic; associated with exposure to food, venom, latex, drug or environmental allergen; attacks typically last 24–48 hr; attacks relieved with antihistamines or corticosteroids	Normal	Normal	Normal	Normal	Normal
NSAID-associated angioedema	Angioedema after ingestion of an NSAID; typically accompanied by urticaria; usually class-specific reaction due to pharmacologic effect of cyclooxygenase inhibition, but allergic in rare instances	Normal	Normal	Normal	Normal	Normal
Angioedema with urticarial vasculitis	Angioedema usually accompanied by urticaria; skin may show petechiae or purpura after resolution of swelling; often there are other symptoms that are consistent with underlying vasculitis	Decreased	Normal	Normal	Decreased	Decreased

* ACE-I denotes angiotensin-converting–enzyme inhibitor, and NSAID nonsteroidal antiinflammatory drug.

ment of abdominal attacks often requires the use of narcotic analgesics; addiction is a concern in patients with frequent attacks, and some patients are inappropriately considered to be "drug seeking." Antiemetic agents and aggressive fluid replacement are also mainstays of therapy.

Management of oropharyngeal attacks focuses on maintaining the patency of the airway. All patients with hereditary angioedema who have an oropharyngeal attack should be closely observed in a facility where rapid intubation or tracheotomy can be performed if necessary. Patients should be closely monitored for evidence of impending airway closure, including a change in voice, loss of the ability to swallow, and difficulty breathing; if any of these develop, elective intubation should be considered. The anatomy of the airway can be highly distorted by the angioedema, so immediate availability of backup tracheotomy is necessary. Direct visualization of the airway is discouraged if immediate airway support is not available, since the trauma of the procedure can worsen the angioedema.

Short-Term Prophylaxis

Short-term prophylactic treatment to prevent attacks of hereditary angioedema is useful in patients with planned exposure to a situation likely to trigger an attack, such as substantial dental work, invasive medical procedures, and surgical procedures. Consensus guidelines based on uncontrolled studies recommend that patients with hereditary angioedema be protected from severe swelling by means of prophylactic treatment with C1 inhibitor (500 to 1500 U given 1 hour before the provoking event) or, when C1 inhibitor is not available, by means of temporarily increasing plasma C1-inhibitor levels through treatment with high-dose 17α-alkylated androgens (e.g., danazol at a dose of 200 mg orally three times a day) for 5 to 10 days before the provoking event or through administration of 2 U of fresh-frozen plasma 1 to 12 hours before the event.[32,33] Although as compared with androgens, fresh-frozen plasma is more expensive and associated with a risk of infection, it is generally considered more effective in preventing or minimizing attacks (in contrast to its uncertain role in the treatment of acute attacks).

Long-Term Prophylaxis

For patients with hereditary angioedema who have frequent or severe attacks, long-term prophylaxis should be considered. Randomized trials have shown that 17α-alkylated androgens and antifibrinolytic drugs significantly reduce the frequency of attacks; patients treated with either agent were attack-free 90% of the time during a 28-day period, as compared with little or none of the time among those receiving placebo. Although the two agents have not been compared head to head, 17α-alkylated androgens appear to be more effective.[34-37] Table 2 shows the drugs and doses commonly used for long-term prophylaxis against attacks of hereditary angioedema. In all patients, the dose should be slowly adjusted to the lowest that provides effective control of the hereditary angioedema, as measured by the clinical response; laboratory tests are not helpful in guiding decisions about the dosage.

Major side effects of 17α-alkylated androgens (cholestatic jaundice, peliosis hepatis, hepatocellular adenomas, and lipid abnormalities) and antifibrinolytic agents (muscle cramps, increased enzyme concentrations in muscle, and potential risk of thrombosis) are dose related and are reviewed in Table 2.[38-41] In patients treated with 17α-alkylated androgens, liver enzyme levels and serum lipid profiles should be monitored regularly (every 6 to 12 months). Because of reports of an association between the prolonged use of 17α-alkylated androgens and liver adenoma or carcinoma,[42,43] periodic liver ultrasonography is recommended for monitoring, particularly in patients with elevated hepatic enzyme levels who have been receiving therapy for more than 10 years. The risk of this complication is not well defined but is of greater concern with longer-term use.

The care of children and pregnant women with hereditary angioedema is complicated by concern about potential adverse effects of 17α-alkylated androgens on growth and development, particularly masculinization of the fetus, premature puberty, and premature closure of epiphyseal plates.[31,44] Antifibrinolytic drugs have therefore been recommended as the first choice in children and pregnant women who require long-term prophylaxis.[44] Nevertheless, there is evidence from uncontrolled trials that low-dose 17α-alkylated androgens can be safely used in children.[44] Oxandrolone has been approved for pediatric use and thus is the preferred 17α-alkylated androgen for the treatment of children.[45]

Patients with hereditary angioedema should be advised to avoid stimuli that may precipitate attacks. Because angiotensin-converting–enzyme inhibitors slow the catabolism of bradykinin,

Table 2. Drugs Commonly Used as Long-Term Prophylaxis for Hereditary Angioedema.*

Drug Class and Name	Usual Adult Dose (Range)	Usual Pediatric Dose (Range)	FDA-Approved for Hereditary Angioedema		Side Effects
			Adults	Children	
17α-Alkylated androgens					
Danazol (Danocrine, Sanofi–Synthelabo)	200 mg/day (100 mg every 3 days–600 mg/day)	50 mg/day (50 mg/wk–200 mg/day)	Yes	No	Common: weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, increase in liver enzymes, hypertension, and alterations in lipid profile Uncommon: decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma
Stanozolol (Winstrol, Winthrop)	2 mg/day (1 mg every 3 days–6 mg/day)	0.5–1 mg/day for children <6 yr; 0.5–2 mg/day for children 6–12 yr	Yes	Yes	
Oxandrolone (Oxandrin, Savient Pharmaceuticals)	10 mg/day (2.5 mg every 3 days–20 mg/day)	0.1 mg/kg/day	No	No	
Methyltestosterone (Android, Valeant Pharmaceuticals)	In men only, 10 mg/day (5 mg every 3 days–30 mg/day)	Not recommended for use in children	No	No	
Antifibrinolytic agents					
Epsilon aminocaproic acid (Amicar, Xanodyne Pharmaceuticals)	2 g thrice daily (1 g twice daily–4 g thrice daily)	0.05 g/kg twice daily (0.025 g/kg twice daily–0.1 g/kg twice daily)	No	No	Common: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes Uncommon: thrombosis
Tranexamic acid (Cyklokapron, Pfizer)	1 g twice daily (0.25 g twice daily–1.5 g thrice daily)	20 mg/kg twice daily (10 mg/kg twice daily–25 mg/kg thrice daily)	No	No	

* All the listed drugs are approved by the Food and Drug Administration (FDA) but not necessarily for the indication of hereditary angioedema. Dosage information for danazol is from Farkas et al.[44] and Gompels et al.[53] and for epsilon aminocaproic acid and tranexamic acid is from Agostoni et al.,[31] Farkas et al.,[44] and Gompels et al.[53]

their use is contraindicated in such patients.[46] Similarly, exogenous estrogens (oral contraceptive pills or hormone-replacement therapy) may exacerbate hereditary angioedema as well as familial angioedema with normal C1-inhibitor levels,[6,47] and caution should be exercised in their use. A recent observational study of oral contraceptive use in patients with hereditary angioedema showed that progestin-only oral contraceptives did not worsen the symptoms of hereditary angioedema and might even improve them.[48] Stress is a known precipitant of attacks of hereditary angioedema, and although there is no direct evidence, stress reduction may substantively improve disease control.

AREAS OF UNCERTAINTY

Despite progress in elucidating the biochemical and molecular characteristics of hereditary angioedema, the mechanisms underlying the initiation and resolution of attacks remain unknown. The severity of symptoms of hereditary angioedema is highly variable and does not correlate well with plasma C1-inhibitor levels. Other factors, such as polymorphisms in the bradykinin receptor or contact-system proteins or variations in the level or function of kininases,[49,50] probably modify the severity of the disease, but these factors remain incompletely understood.

Optimal strategies for managing acute attacks still need to be defined. Five new drugs (Table 3) have been studied in phase 3 clinical trials for the treatment of hereditary angioedema,[51] although none are currently approved by the Food and Drug Administration. All have shown significant efficacy in the treatment of acute attacks, and one (nanofiltered C1 inhibitor) also provided a significant benefit as long-term prophylaxis. Further data are needed to inform the role of these agents in practice. Questions include whether drugs targeting the bradykinin pathway alone (ecallantide and icatibant) are as effective as C1-inhibitor replacement therapy, whether recombinant C1 inhibitor is as effective as plasma-derived C1 inhibitor, whether there

Table 3. New Drugs under Investigation for Treatment of Hereditary Angioedema.

Drug	Potential Indications	Dose	Mechanism*	Anticipated Potential Side Effects
Plasma-derived nanofiltered C1 inhibitor (Cinryze, Lev Pharmaceuticals)	Acute attacks, short-term prophylaxis, long-term prophylaxis	1000 U intravenously	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: anaphylaxis Theoretical: transmission of infectious agent
Plasma-derived C1 inhibitor (Berinert-P, CSL Behring)	Acute attacks, short-term prophylaxis, long-term prophylaxis	20 U per kg intravenously	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: anaphylaxis Theoretical: transmission of infectious agent
Recombinant human C1 inhibitor (Rhucin, Pharming)	Acute attacks, short-term prophylaxis	50–100 U per kg intravenously	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Uncommon: anaphylaxis
Ecallantide (Dyax)†	Acute attacks	30 mg subcutaneously	Inhibits plasma kallikrein	Common: prolonged partial-thromboplastin time Uncommon: development of antidrug antibodies, anaphylaxis
Icatibant (Firazyr, Jerini)	Acute attacks	30 mg subcutaneously	Bradykinin B2 receptor antagonist	Common: discomfort at injection site

* MASP denotes mannose-binding lectin–associated serine protease.
† There is currently no trade name for ecallantide.

are clinically relevant differences in the responses to these drugs, and which patients would benefit from long-term prophylaxis with C1 inhibitor. Additional studies are needed to determine the value of prophylactic treatment as compared with on-demand treatment for acute attacks as well as to assess the benefits and risks of allowing patients to use these new drugs at home to treat attacks at an early point in their course.[52] The optimal approach to the diagnosis and treatment of inherited angioedema with normal C1 inhibitor levels remains unknown.

GUIDELINES

Consensus guidelines regarding the diagnosis and management of hereditary angioedema have recently been published.[53] The recommendations in this article are generally consistent with these guidelines, except that plasma-derived C1 inhibitor is unavailable in the United States.

CONCLUSIONS AND RECOMMENDATIONS

The presentation of the young woman described in the vignette is consistent with an abdominal attack of hereditary angioedema. The escalation in attack frequency may be related to the use of an oral contraceptive. A detailed family and personal history generally suggests the diagnosis of hereditary angioedema and reduces the likelihood of inappropriate surgical intervention for abdominal pain. Measurement of the C4 level is an effective screening test for hereditary angioedema; documentation of a low level should be followed by measurement of the C1-inhibitor level and the C1 level to confirm the clinical diagnosis and rule out acquired C1-inhibitor deficiency. Patients with hypotension and severe abdominal pain, like the woman in the vignette, need to be hospitalized and treated with aggressive intravenous hydration to restore vascular volume, pain medications (including narcotics if necessary), and antiemetic agents. I would advise this patient to discontinue her oral contraceptive pills and use nonhormonal means of contraception or possibly a progestin-only oral contraceptive. Given the severity of her attacks, I would prescribe a medication to reduce the frequency of attacks; I generally start with low-dose danazol, typically 100 mg per day in young women, with an increase or decrease in the dose after 1 month, depending on the initial response. The course of hereditary angioedema is unpredictable; the danazol dose may need to be increased (to 200 mg per day) or slowly

tapered and stopped. Finally, the patient should be given a card to keep with her that identifies her as having hereditary angioedema and contains information about appropriate emergency treatment.

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